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(21) International Application Number: PCT/US00/11092 (22) International Filing Date: 21 April 2000 (21.04.2000) (30) Priority Data: 09/298,545 23 April 1999 (23.04.1999) US (60) Parent Application or Grant HEALTHSHIELD TECHNOLOGIES L.L.C. [/]; (). BARRY, John, E. [/]; (). TROGOLO, Jeffrey, A. [/]; (). TODARO, John, C.; ().	Published	
(54) Title: STENT HAVING ANTIMICROBIAL AGENT (54) Titre: EXTENSEUR POURVU D'UN AGENT ANTIMICROBIEN (57) Abstract <p>A medical stent having an inorganic antimicrobial agent on a surface, the agent preferably being a zeolite. The stent can be of metal or a polymer and the agent being in a coating that is applied to one or both of the surfaces of the stent. The stent can be of a polymer resin incorporating the agent.</p> (57) Abrégé <p>L'invention concerne un extenseur médical dont une surface est pourvue d'un agent antimicrobien inorganique, l'agent étant de préférence un zéolite. L'extenseur peut être fait d'un métal ou d'un polymère et l'agent peut se présenter comme un revêtement appliqué à une ou aux deux surfaces de l'extenseur. L'extenseur peut être en résine polymère avec l'agent incorporé.</p>		

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(21) International Application Number: PCT/US00/11092 (22) International Filing Date: 21 April 2000 (21.04.00) (30) Priority Data: 09/298,545 23 April 1999 (23.04.99) US (71) Applicant: HEALTHSHIELD TECHNOLOGIES L.L.C. [US/US]; Suite 201, 67 Prospect Avenue, West Hartford, CT 06106 (US). (72) Inventors: BARRY, John, E.; 18 Drake Lane, Derry, NH 03038 (US). TROGOLO, Jeffrey, A.; 228 Commonwealth Avenue, Boston, MA 02116 (US). (74) Agents: TODARO, John, C. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022-7513 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: STENT HAVING ANTIMICROBIAL AGENT (57) Abstract A medical stent having an inorganic antimicrobial agent on a surface, the agent preferably being a zeolite. The stent can be of metal or a polymer and the agent being in a coating that is applied to one or both of the surfaces of the stent. The stent can be of a polymer resin incorporating the agent.		

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Description

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5 STENT HAVING ANTIMICROBIAL AGENT

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Field of the Invention

The invention relates to a medical stent having antimicrobial properties.

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Background of the Invention

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Stents are devices widely used in the medical field. For example, there are coronary and peripheral artery stents made of metal, such as stainless steel, NiTi or tungsten. Typical of these are of the type shown in U.S. patent 5,690,670. These stents also can be of metal coated with a polymer, such as polyurethane, or coated with a material such as silicone rubber. Typical of these are stents shown in U.S. Patent 5,713,949. Biliary, + esophageal, urinary and urethral stents often are of polymeric material. Stents of a polymer material are shown in U.S. Patents 5,713,949 and 5,607,467.

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Most, if not all, of such stents are subject to contact with body fluids, such as blood, and with body tissue, such as arterial vessels. The materials contacting the stent are potential sources of contamination by bacteria. Also, the stent itself is a potential site for bacteria growth. Therefore, it would be desirable to provide the stent with antimicrobial properties. That is, it would be desirable that bacteria in the body fluids and tissue contacting the stent are killed. Providing the antimicrobial properties preferably should be done in a manner which does not increase build-up of solid materials deposited on the stent and, more preferably, should reduce such build-up. Also, providing the stent with antimicrobial properties should

5 not adversely affect the stent deployment characteristics or its mechanical properties.

The general subject of attempting to provide antimicrobial action for medical type products to be used in the body has been considered. For example, U.S. Patent 5,906,466 describes an antimicrobial composition comprising antimicrobial silver compounds deposited on a physiologically inert oxide support material. In Japanese patent abstract No. 08041611 an alloy exhibiting antimicrobial properties is disclosed.

10 Brief Description of the Invention

The present invention relates to a medical stent having antimicrobial properties. For a metal stent, in one embodiment a coating of a material with the antimicrobial agent is applied to the stent. For example, for the metal stent, the coating is of an adhesive type material, such as a hydrophilic polyurethane, which contains the antimicrobial agent. In another embodiment of a metal stent, the agent is applied to the metal stent as a powder coating. The coating can be applied to either both of the stent inner and outer surfaces.

For polymer stents, the agent can be blended into the polymeric resin that forms the stent. Thus, antimicrobial agent is present on both the stent inner and outer surfaces. Here also, a stent of resin material can have a coating containing the agent applied to one or both of its inner and outer surfaces.

In a preferred embodiment of the invention, the antimicrobial agent is of inorganic material, preferably a zeolite.

45 Objects of the Invention

It is therefore an object of the invention to provide a medical stent having antimicrobial properties.

Another object is to provide a medical stent one or both of whose inner and outer surfaces is coated with an inorganic antimicrobial

5 agent.

A further object is a medical stent containing a zeolite as an antimicrobial agent.

10 Still an additional object is to provide a medical stent made of
5 resin containing an inorganic antimicrobial agent.

Yet another object is to provide a medical stent having a coating containing an inorganic antimicrobial agent.

Brief Description of the Drawings

10 Other objects and advantages of the present invention will
20 become more apparent upon reference to the following specification and annexed drawings in which:

Fig. 1 is a view of a typical medical stent of metal; and

25 Figs. 2 and 3 respectively show a plan view of a blank of
15 material for a stent and a stent made from the blank.

Detailed Description of the Invention

30 Fig. 1 shows a metal stent of the type disclosed in U.S. Patent 5,690,670. This is illustrative of any type of metal stent with which the
20 present invention can be utilized. The stent 160 of Fig. 1 is of the
35 expandable type and is shown in a non-expanded state positioned on the distal end of a balloon expandable segment 162 of a guide wire 164. The
40 stent 160 is fabricated from a suitable material such as stainless steel, NiTi, tungsten, Ti-Nb-Zr alloy or any other suitable material. The stent illustrated is
25 designed so that it can be collapsed over a balloon segment of a balloon catheter.

45 The stent is positioned within a segment of a tubular body conduit 165, a blood vessel for example, to be propped open. Expansion of
the balloon 162 expands the stent 160 radially outward up to the blood
30 vessel wall 166 so that means for gripping soft tissue, such as barbs (not
50 shown), on the outer surface of the stent 160, engage and grip blood vessel

5 tissue to anchor the stent 160 in position. The balloon 162 is then collapsed
and removed leaving the stent. In this way, the blood vessel is permanently
10 propped open. As seen, the stent is in a position where it is contacted both
by blood and body tissue.

5 In accordance with the invention one or both of the stent inner
and outer surfaces has a coating 200 of a material containing an antimicrobial
15 agent, which is described in detail below. It is preferred that at least the
outer surface be coated with the material containing the agent since this
comes into contact with the body tissue. The process for coating and the
10 material are described below.

20 The metal stent described in Fig. 1 for a blood vessel is only
illustrative of the type of stent with which the subject invention can be
employed. It is also applicable to urinary, gastrointestinal, and other stent
25 applications. The stent can be of any shape, size and metal suitable for the
15 application.

Figs. 2 and 3 show a stent of the type disclosed in U.S. Patent
30 5,713,949. As shown from Fig. 2, the stent starts as a flat piece of material
1 that has a top edge 2, a bottom edge 3 and ends 4 and 5. The piece 1
includes rows of slots 6, 7 which are offset from each other. The material of
20 piece 1 is a resin, such as polyethylene, polyurethane, polytetrafluoroethylene,
35 silicone, block co-polymers of polyurethane and other suitable resins. These
materials can be molded in a suitable die to produce the desired shape and
slots 6, 7.

40 As seen in Fig. 2, the piece 1 is formed into a cylindrical stent
25 with the edges 2, 3 attached together by any suitable means such as, for
example, by surface fusing, ultrasonic welding or any other suitable
technique. It should be noted that the material for piece 1 can be of metal.
45 Here, the slots 6, 7 can be formed by laser etching or other suitable
technique.

30 For stents of a polymer material the agent can be incorporated
50 directly into the resin used to make the stent. A coating containing the agent

also can be applied to one or both of its surfaces.

Processes for making the different types of stents are described below.

Coated Stents - For a metal stent, the inorganic antimicrobial agent preferably is applied as a coating. A coating with the agent also can be applied to a stent of polymeric material, such as of Figs. 2 and 3. In either case, the coating must be adherent and flexible, the latter to accommodate flexing, bending and compression of the stent. Typical thickness for the coatings are from between about 1 - 15 microns, preferably, between about 1 - 10 microns and most preferably between about 1 - 5 microns.

Coatings of a polymer containing the agent are preferred for both the metal and polymeric stents. These can be bonded to the stent, that is, the coating is effectively adhesively bonded to the stent. The polymers for the coating can be of silicone rubber and hydrophilic polymers. A preferred coating can be of, for example, a hydrophilic polymer such as hydrophilic polyurethane or a hydrophilic polymer material having a lubricious property, such as shown in U.S. Patent 5,731,087. The antimicrobial agent preferably comprises zeolite ceramic particles mixed with the coating material. That is, the zeolite particles are blended in the desired amount into the coating material.

The agent particles comprise by weight of the coating between about 0.1% - 100% , more preferably between about 0.1% - 75% and most preferably between about 0.5%-50.0%. The size of the particles of the agent is preferably about 1.0 micron in nominal diameter.

The coating with the agent is applied by any suitable technique, such as spraying, painting or dipping the metal or resin stent into the coating material. This can be done either while the material piece forming the stent is flat or after it has its cylindrical shape. By using painting or spraying the coating with the agent can be applied to only one of the stent inner or outer surfaces. Heat and/or pressure is applied and roughening or etching of the surface is performed as needed depending upon the stent and coating

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materials.

1. Polymeric stent with coating:

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resin for stent

any suitable resin such as
polyurethane, polyvinylchloride

coating

Hydrophilic polyurethane, silicone
rubber adhesives

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agent

0.1 to 5.0 wt% Ag in zeolite

wt%

0.1 to 100.0, more preferably 0.5 to
75.0 and most preferably 1.0 to 50.0
of agent in the coating

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size of agent particles

1.0 microns

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2. Metal stent that is coated:

stent material

NiTi, stainless steel, Ti-Nb-Zn,
tungsten, tantalum

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coating

hydrophilic polyurethane, silicone
rubber adhesives

agent

0.1 to 5.0 wt% in Ag in zeolite

35

30

wt%

0.1 to 100.0, more preferably 0.5 to
75.0 and most preferably 1.0 to 50.0
of agent in the coating

size of agent particles

1 micron

40

35

3. Metal stent with resin coating containing antimicrobial agent:

stent material

NiTi, stainless steel, TiNb-Zn, tungsten,
tantalum

45

40

coating

hydrophilic polyurethane, silicone
rubber adhesives

50

45

agent

0.1 to 5.0 wt% Ag in zeolite

55

5		wt%	0.1 to 20.0, more preferably 0.5 to 10.0 and most preferably 0.5 to 5.0 of agent in the coating
10	5	size of agent particles	1.0 micron

Metal stents 2 and 3 above involve coating the metal with the polymer leaving the spaces 6, 7 of Figs. 2 and 3 between the metal struts free. In contrast, metal stent 3 above is a metal stent that is completely covered by a polymer containing the zeolite.

For a metal stent, a powder coating process also can be used to apply the coating containing the antimicrobial agent. A powder coating process usually comprises the basic steps of cleaning the metal, electrostatically spraying the powder onto the metal, and baking. One or both of the stent surfaces can be powder coated. Here, particles of the inorganic antimicrobial, such as the ceramic particles, can be incorporated into the powder, blended directly with the powder or applied in a second step to the surface of a powder coated part before the baking step.

Incorporation of the inorganic antimicrobial agent into the powder to be sprayed can be accomplished in any suitable way. For example, it can be done by preparing a master batch concentrate of the resin particles containing the agent particles. That is, the zeolite ceramic particles are also made in a base resin, such as polyethylene, polyurethane, etc. These resin particles containing the zeolite ceramic, are then blended into the polymer or coating material, such as by kneading or rolling to form pellets having the agent in a desired concentration. This preferably is between 0.1 to 30% by weight, preferably 0.5 to 15%, and most preferably 1 to 10% of the pellets. The size of the resin containing zeolite particles in the pellets preferably is about 1.0 micron. The pellets are then ground or melt atomized to produce a powder that is used directly in the spray powder coating process. Also, the mixture can be diluted with untreated powder normally used in the conventional powder coating process. An illustration of a metal stent that is powder coated follows.

4. Metal stent that is powder coated:

stent material	NiTi, stainless steel, Ti-Nb-Zn, tungsten, tantalum
powder	silica
agent	0.1 to 5.0 wt% Ag in zeolite
wt% of zeolite in powder	0.1 to 100.0, more preferably 0.5 to 75.0 and most preferably 1.0 to 50.0 of agent in the powder for coating
size of agent particles	1.0 micron

An alternate method is to combine untreated polymer powder with a solution of an appropriate solvent, with or without a binder, and particles of the inorganic antimicrobial to coat the polymer powder particles with the inorganic antimicrobial agent particle. The solvent is then evaporated and the resulting powder composite is used in the conventional powder coating process ensuring that the inorganic antimicrobial is exposed at the surface. Here, the particle size of the ceramic resin particles of the agent also preferably is about 1.0 micron nominal diameter.

Another method of producing an antimicrobial powder coating is to apply a polymer powder in the conventional manner to the stent surface or surfaces and then apply particles of the inorganic antimicrobial agent in a solvent or water. The stent is then dried and, as in the conventional powder coating process, the inorganic antimicrobial agent is incorporated onto the surface of the coating. Here, the size of the particles of the agent is preferably from about 0.8 to 2.0 microns nominal diameter.

In all of the above coating processes for both the metal and resin type stents, the inorganic antimicrobial agent is present on one or both of the stent surface to perform the intended function of killing bacteria.

Polymeric Stent With Agent - As explained with respect to Figs. 2 and 3, the stent can be of a polymeric material that is prepared from a

5 suitable resin mixture containing the agent. Here, the agent is automatically available on both surfaces of the stent.

10 These resins with the agent can be prepared by first preparing a master batch concentrate of the antimicrobial agent. That is, particles of the ceramic zeolite in the resin base are blended with a polymeric resin, such as
5 by kneading or molding. This master batch material is formed into pellets, which can be ground to any desired size. Methods for incorporating the antibiotic agent in the resin are described in U.S. Patents Nos. 4,938,955 and
15 4,906,464. Final formation of the stents from the resin incorporating the antimicrobial agent can be by compression molding or other conventional forming methods.
20

The pellets of the master batch material is then added to untreated resin that is to be used to make the stent. The composite of the
25 master batch and untreated resin preferably results in a final concentration by weight of between 0.1 to 30%, preferably 0.5 to 15%, most preferably 1 to 10% of the agent zeolite particles. An example of a polymeric stent follows.

30 5. Polymeric stent:

20	resin	polyurethane, polyvinylchloride, silicone rubber
35	agent	Ag in zeolite (AJ10N Shinagawa)
25	wt%	0.1 to 20.0, more preferably 0.5 to 10.0 and most preferably 0.5 to 5.0 of agent in the resin of the stent
40	size of agent particles	1.0 micron
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45 Where polyurethane is to be used as the resin material for the stent, the polyurethane is in liquid form. The zeolite particles, preferably in a base polyurethane resin form but also in the normal ceramic particle state, can
35 be added to untreated polyurethane liquid to make a master batch concentrate, which is then added to untreated polyurethane to make the resin
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5 to be formed into the stent. Alternatively, the zeolite particles in resin form or
as the ceramic particles can be added directly into untreated polyurethane.
The liquid polyurethane with the particles of the agent are then molded to
10 make the stent. The stent has the agent throughout its entire body and on
5 both surfaces.

The antibiotic particles are preferably present in a concentration
by weight in the resin used to make the stent of from 0.01 to 10.0wt%,
15 more preferably from 0.01 to 8.0 wt%, and most preferably from 0.1 to 5.0
wt%. They are present on the surfaces of the stent contacted by the body
10 fluid or body tissue.

20 A preferred embodiment of the resin with agent for making a
polymeric stent has the following constituents:

25	15	plastic resin type	polyurethane
		material of agent	silver zeolite (preferably Shinagawa type AJ10N)
30	20	wt.% of agent in composite of the stent	1.0%
		size of the agent particles	0.8 - 25.0 microns

35 25 While specific amounts of the antimicrobial agent are given for
the various types of stents, it should be considered that in each case that
there is an amount of the agent that is sufficient to produce an effective
40 concentration. This means that there is a sufficient amount of the
antimicrobial agent used alone, added to or combined with other materials
30 such as to prevent or inhibit the growth of bacterial and/or fungal organisms
or to kill such organisms in the particular stent application. The amount of
45 the agent will vary based on the specific agent used and the material with
which it is mixed or added to and upon known factors such as type and use
of the stent. Environmental factors such as body temperature also should be
50 35 taken into consideration. It is within the ability of one skilled in the art to

5 relatively easily determine an effective amount of the antimicrobial agent to be used with each material.

10 As to the inorganic antimicrobial agent incorporated in the resin for the stent, into the liquid coating material or used in the coating powder, a number of metal ions, which are inorganic materials, have been shown to possess antibiotic activity, including silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium and thallium ions. These antibiotic metal ions are believed to exert their effects by disrupting respiration and electron transport systems upon absorption into bacterial or fungal cells. Antimicrobial metal ions (cations) of silver, gold, copper and zinc, in particular, are considered safe even for *in vivo* use. Antimicrobial silver cations are particularly useful for *in vivo* use due to the fact that they are not substantially absorbed into the body. That is, if such materials are used they should pose no hazard.

15 In one embodiment of the invention, the inorganic antibiotic metal containing composition is an antibiotic metal salt. Such salts include silver acetate, silver benzoate, silver carbonate, silver ionate, silver iodide, silver lactate, silver laureate, silver nitrate, silver oxide, silver palpitae, silver protein, and silver sulfadiazine. Silver nitrate is preferred. These salts are particularly quick acting, as no release from ceramic particles is necessary to function antimicrobially.

20 Antibiotic ceramic particles useful with the present invention include zeolites, hydroxy apatite, zirconium phosphates or other ion-exchange ceramics. Zeolites are preferred, and are described in the preferred embodiments referred to below. Hydroxy apatite particles containing antimicrobial metals are described, e.g., in U.S. Patent No. 5,009,898. Zirconium phosphates containing antimicrobial metals are described, e.g., in U.S. Patent Nos. 5,296,238; 5,441,717; and 5,405,644.

25 Inorganic particles, such as the oxides of titanium, aluminum, zinc and copper, may be coated with a composition which confers antimicrobial properties, for example, by releasing antimicrobial metal ions

5 such as silver ions, which are described, e.g., in U.S. Patent No. 5,180,585. Inorganic soluble glass particles containing antimicrobial metal ions, such as silver, are described, e.g., in U.S. Patent Nos. 5,766,611 and 5,290,544.

10 Antibiotic zeolites are preferred. These have been prepared by
5 replacing all or part of the ion-exchangeable ions in zeolite with ammonium ions and antibiotic metal ions, as described in U.S. Patent Nos. 4,938,958 and 4,911,898. Such zeolites have been incorporated in antibiotic resins (as
15 shown in U.S. Patent Nos. 4,938,955 and 4,906,464) and polymer articles (U.S. Patent No. 4,775,585). Polymers including the antibiotic zeolites have
10 been used to make refrigerators, dish washers, rice cookers, plastic film, chopping boards, vacuum bottles, plastic pails, and garbage containers. Other
20 materials in which antibiotic zeolites have been incorporated include flooring, wall paper, cloth, paint, napkins, plastic automobile parts, catheters, bicycles, pens, toys, sand, and concrete. Examples of such uses are described in US
25 Patents 5,714,445; 5,697,203; 5,562,872; 5,180,585; 5,714,430; and 5,102,401. These applications involve slow release of antibiotic silver from the zeolite particles.

30 Antibiotic zeolites are well-known and can be prepared for use in the present invention using known methods. These include the antibiotic
20 zeolites disclosed, for example, in U.S. Patent Nos. 4,938,958 and 4,911,898.

35 Either natural zeolites or synthetic zeolites can be used to make the antibiotic zeolites used in the present invention. "Zeolite" is an aluminosilicate having a three dimensional skeletal structure that is
40 represented by the formula: $XM_{2n}O \cdot Al_2O_3 \cdot YSiO_2 \cdot ZH_2O$. M represents an ion-exchangeable ion, generally a monovalent or divalent metal ion, n represents the atomic valency of the (metal) ion, X and Y represent
45 coefficients of metal oxide and silica respectively, and Z represents the number of waters of crystallization. Examples of such zeolites include A-type
30 zeolites, X-type zeolites, Y-type zeolites, T-type zeolites, high-silica zeolites, sodalite, mordenite, analcite, clinoptilolite, chabazite and erionite. The present
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invention is not restricted to use of these specific zeolites.

The ion-exchange capacities of these zeolites are as follows:

A-type zeolite = 7 meq/g; X-type zeolite = 6.4 meq/g; Y-type zeolite = 5 meq/g; T-type zeolite = 3.4 meq/g; sodalite = 11.5 meq/g; mordenite = 2.6 meq/g; analcite = 5 meq/g; clinoptilolite = 2.6 meq/g; chabazite = 5 meq/g; and erionite = 3.8 meq/g. These ion-exchange capacities are sufficient for the zeolites to undergo ion-exchange with ammonium and antibiotic metal ions.

The specific surface area of preferred zeolite particles is preferably at least 150 m²/g (anhydrous zeolite as standard) and the SiO₂/Al₂O₃ mol ratio in the zeolite composition is preferably less than 14, more preferably less than 11.

The antibiotic metal ions (cations) used in the antibiotic zeolites should be retained on the zeolite particles through an ion-exchange reaction. Antibiotic metal ions which are adsorbed or attached without an ion-exchange reaction exhibit a decreased bactericidal effect and their antibiotic effect is not long-lasting. Nevertheless, it is advantageous for imparting quick antimicrobial action to maintain a sufficient amount of surface adsorbed metal ion.

In the ion-exchange process, the antibiotic metal ions tend to be converted into their oxides, hydroxides, basic salts etc. either in the micropores or on the surfaces of the zeolite and also tend to deposit there, particularly when the concentration of metal ions in the vicinity of the zeolite surface is high. Such deposition tends to adversely affect the bactericidal properties of ion-exchanged zeolite.

In an embodiment of the antibiotic zeolites, a relatively low degree of ion exchange is employed to obtain superior bactericidal properties. It is believed to be required that at least a portion of the zeolite particles retain metal ions having bactericidal properties at ion-exchangeable sites of the zeolite in an amount less than the ion-exchange saturation capacity of the zeolite. In one embodiment, the zeolite employed in the present invention

5 retains antimicrobial metal ions in an amount up to 41% of the theoretical
ion-exchange capacity of the zeolite. Such ion-exchanged zeolite with a
relatively low degree of ion-exchange may be prepared by performing
10 ion-exchange using a metal ion solution having a low concentration as
5 compared with solutions conventionally used for ion exchange.

The antibiotic metal ion is preferably present in the range of from
about 0.1 to 20.0 wt.% of the zeolite. In one embodiment, the zeolite
15 contains from 0.1 to 20.0 wt.% of silver ions and from 0.1 to 20.0 wt.% of
copper or zinc ions. Although ammonium ion can be contained in the zeolite
10 at a concentration of about 20.0 wt.% or less of the zeolite, it is desirable to
20 limit the content of ammonium ions to from 0.5 to 15.0 wt.%, preferably 1.5
to 5.0 wt.%. Weight% described herein is determined for materials dried at
temperatures such as 110°C, 250°C or 550°C as this is the temperature
25 employed for the preferred post-manufacturing drying process.

15 A preferred antibiotic zeolite is type A zeolite containing either a
combination of ion-exchanged silver, zinc, and ammonium or silver and
ammonium. One such zeolite is manufactured by Shinagawa, Inc. under the
30 product number AW-10N and consists of 0.6% by weight of silver ion-
exchanged in Type A zeolite particles having a diameter of about 2.5 μ .
20 Another formulation, AJ-10N, consists of about 2% by weight silver ion-
35 exchanged in Type A zeolite particles having a diameter of about 2.5 μ .
Another formulation, AW-80, contains 0.6% by weight of silver ion-
exchanged in Type A zeolite particles having a diameter of about 1.0 μ .
40 Another formulation, AJ-80N, consists of about 2% by weight silver ion-
25 exchanged in Type A zeolite particles having a diameter of about 1.0 μ . These
zeolites preferably contain about between 0.5% and 2.5% by weight of ion-
exchanged ammonium. Other formulations also are available.

45 The zeolites are often obtained in master batches of low density
polyethylene, polypropylene, or polystyrene, containing about 20.0 wt.% of
30 the zeolite. Thus, they can be easily mixed with the resins used as materials
50 for forming the composite resin used to make the stent or in the liquid coating

5 material.

The antibiotic properties of the antibiotic zeolite particles of the invention may be assayed while in aqueous formulations using conventional assay techniques, including for example determining the minimum growth
10 inhibitory concentration (MIC) with respect to a variety of bacteria, eumycetes and yeast. In such a test, the bacteria listed below may be employed:
15 such a test, the bacteria listed below may be employed:

Bacillus cereus varmycoides;

Escherichia coli;

10 *Pseudomonas aeruginosa;*

20 *Staphylococcus aureus;*

Streptococcus faecalis;

Aspergillus niger;

Aureobasidium pullulans;

25 15 *Chaetomium globosum;*

Glocladium virens;

Penicillium funiculosum;

Candida albicans; and

30 *Saccharomyces cerevisiae.*

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The assay for determining MIC can be carried out by smearing a solution containing bacteria for inoculation onto a plate culture medium to which a test sample of the encapsulated antibiotic zeolite particles is added in a particular concentration, followed by incubation and culturing of the plate.
35 The MIC is defined as a minimum concentration thereof required for inhibiting the growth of each bacteria.
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Safety and biocompatibility tests were conducted on the antibiotic zeolites employed in the invention. ISO 10993-1 procedures were employed. The following results were obtained:
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Cytotoxicity: Non-Toxic
Acute Systemic Toxicity: Non-Toxic
Oral Toxicity: Safer than table salt
Intracutaneous Toxicity: Passed
Skin Irritation Test: Non-Irritant
Chronic Toxicity: No Observable Effect
<i>In-vitro</i> Hemolysis: Non-Hemolytic
30-day Muscle Implant Test: Passed
60-day Muscle Implant Test: Passed
90-day Muscle Implant Test: Passed
Ames Mutagenicity Test: Passed
Pyrogenicity: Non-Pyrogenic

Thus, the antibiotic zeolites are exceptionally suitable under relevant toxicity and biocompatibility standards for use in the stents.

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Specific features of the invention are shown in one or more of the drawings for convenience only, as each feature may be combined with other features in accordance with the invention. Alternative embodiments will be recognized by those skilled in the art and are intended to be included within the scope of the claims. All patent applications, patents, patent publications, and literature references cited in this specification are hereby incorporated by reference in their entirety. In the case of inconsistencies, the present description, including definitions, is intended to control. Accordingly, the above description should be construed as illustrating and not limiting the scope of the invention. All such obvious changes and modifications are within the patented scope of the appended claims.

Claims

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We Claim:

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- 1 1. A medical stent comprising a metal, said stent having at
2 least one surface which is to be contacted by body tissue or body fluid
3 wherein said surface is coated with a composition containing antimicrobial
4 zeolite particles.

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- 1 2. The medical stent of claim 1, wherein said metal is
2 selected from the group consisting of stainless steel, NiTi, tungsten, Ti-Nb-Zr
3 alloy and tantalum.

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- 1 3. The medical stent of claim 1 wherein said zeolite particles
2 comprise from 0.5 to 75.0 wt. % of said composition.

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- 1 4. The medical stent of claim 3 wherein said zeolite particles
2 comprise from 0.1 to 20.0 wt. % of the resin stent.

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- 1 5. The medical stent of claim 1 wherein said composition
2 comprises a polymeric resin.

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- 1 6. The medical stent of claim 5, wherein said polymeric resin
2 is selected from the group consisting of hydrophilic polyurethane and silicone
3 rubber adhesives.

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- 1 7. The medical stent of claim 1, wherein said composition is
2 coated on each of the inner and outer surfaces of said stent.

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- 1 8. The medical stent of claim 1, wherein said antimicrobial
2 zeolite particles comprise antimicrobial metal cations.

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- 1 9. The medical stent of claim 7 wherein said antimicrobial
2 metal ions are silver ions present in the form of a silver salt.

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1 10. The medical stent of claim 1 wherein said zeolite particles
2 are from 0.5 to 2.5 microns.

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1 11. A medical stent comprising a polymeric resin, and
2 antimicrobial zeolite particles, said stent having at least one surface which is
3 to be contacted by body tissue or body fluid.

15

1 12. The medical stent of claim 11, wherein said zeolite
2 particles are coated on at least one surface of said stent.

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1 13. The medical stent of claim 11, wherein said polymeric
2 resin is selected from the group consisting of polyurethane and polyvinyl
3 chloride.

25

1 14. A medical stent comprising a metal, said stent having at
2 least one surface which is to be contacted by body tissue or body fluid
3 wherein said surface is coated with a composition which comprises a
4 coating containing an inorganic antimicrobial agent.

30

1 15. The stent of claim 14, wherein said antimicrobial agent
2 contains silver cations as the active ingredient.

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1 16. The sten of claim 14, wherein said antimicrobial agent
2 comprises a ceramic carrier.

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1 17. A medical stent comprising a polymeric resin, and an
2 inorganic antimicrobial agent, said stent having at least one surface which is
3 to be contacted by body tissue or body fluid.

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1 18. The stent of claim 17, wherein said antimicrobial agent
2 contains silver cations as the active ingredient.

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1 19. The sten of claim 17, wherein said antimicrobial agent
2 comprises a ceramic carrier.

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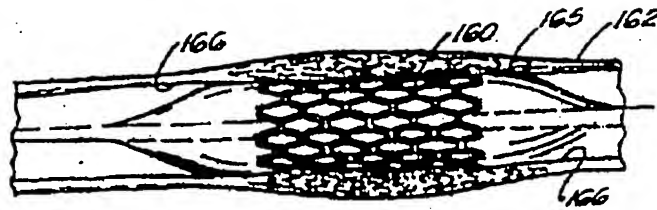
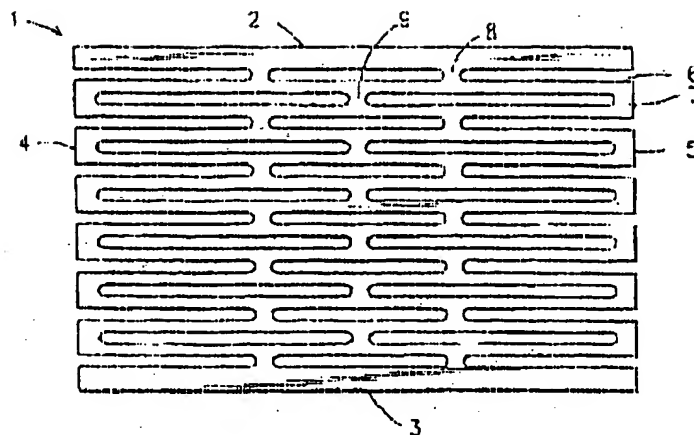


FIGURE 1

**FIGURE 2**

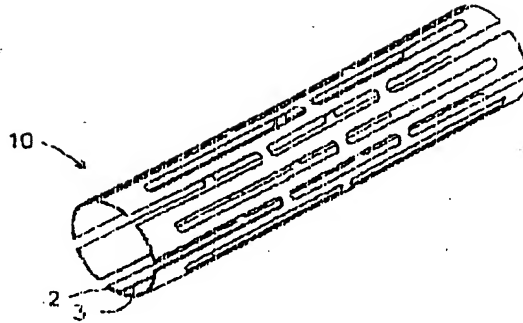


FIGURE 3

Inter. nal Application No
PCT/US 00/11092

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B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 31709 A (UNIV NEW YORK) 4 September 1997 (1997-09-04) page 9, line 18 - line 20 page 15, line 34 claims	1,3-19
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Y Further documents are listed in the continuation of box C.

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24 August 2000

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05/09/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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WO 0030697 A	02-06-2000	NONE	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 29/00, A61L 31/00	A1	(11) International Publication Number: WO 00/18446 (43) International Publication Date: 06 April 2000 (06.04.2000)
(21) International Application Number: PCT/EP99/07156 (22) International Filing Date: 27 September 1999 (27.09.1999) (30) Priority Data: 98402367.1 25 September 1998 (25.09.1998) EP (60) Parent Application or Grant LABORATOIRES NYCOMED S.A. [/]; O. BESSIERE, Fabienne [/]; O. STROHBAND, Hans-Peter [/]; O. ANDERSEN, Erik [/]; O. BESSIERE, Fabienne [/]; O. STROHBAND, Hans-Peter [/]; O. ANDERSEN, Erik [/]; O. BOYDELL, John, Christopher ; O.	Published	
(54) Title: MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE (54) Titre: MANCHON MULTICOUCHE POUR DISPOSITIF INTRAVASCULAIRE EXPANSIBLE (57) Abstract <p>The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.</p> (57) Abrégé <p>La présente invention concerne un manchon multicouche destiné à envelopper un dispositif expansible devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Plus particulièrement, la présente invention concerne un manchon (1, 2) multicouche de libération d'agents thérapeutiques destiné à envelopper un dispositif (3) expansible tel qu'une prothèse endovasculaire devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Ainsi, la présente invention peut être d'abord appliquée au traitement de troubles dans des canaux du corps comprenant une paroi de canal et une lumière par laquelle s'écoule un fluide corporel. L'oesophage, l'urètre, et les vaisseaux sanguins coronaires et périphériques constituent des exemples de ces canaux du corps.</p>		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61L 29/00, 31/00	A1	(11) International Publication Number: WO 00/18446 (43) International Publication Date: 6 April 2000 (06.04.00)
(21) International Application Number: PCT/EP99/07156 (22) International Filing Date: 27 September 1999 (27.09.99) (30) Priority Data: 98402367.1 25 September 1998 (25.09.98) EP (71) Applicant (for all designated States except US): LABORATOIRES NYCOMED S.A. [FR/FR]; Centre d'Affaires et d'Activites, "Tolbiac Massena", 25, quai Panhard Levasor, F-75013 Paris (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): BESSIERE, Fabienne [FR/FR]; 1, avenue Gallieni, F-94100 Saint Maur (FR). STROHBAND, Hans-Peter [DE/DE]; Carl Zuckmayer Strasse 32, D-40699 Erkrath (DE). ANDERSEN, Erik [DK/DK]; Ronnens Kut 5, DK-4000 Osted Roskilde (DK). (74) Agents: BOYDELL, John, Christopher et al.; Stevens Hewlett & Perkins, 1 Serjeants' Inn, Fleet Street, London, Greater London EC4Y 1NT (GB).	(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>	
(54) Title: MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE (57) Abstract <p>The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.</p>		

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Description

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MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE

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The present invention relates to a multi-layered sleeve for
5 encompassing an expandable device to be introduced into a body canal,
15 such as a blood vessel for example and to a method of manufacturing such
a sleeve.

More particularly, the present invention relates to a therapeutic
20 agent-releasing multi-layered sleeve for encompassing an expandable
10 device, such as a stent, to be introduced into a body canal, such as a
blood vessel for example.

Hence, the present invention is primarily applicable to the treatment
25 of disorders of body canals comprising a canal wall and a lumen through
which a body fluid flows. Examples of such body canals are the
15 oesophagus, the urethra, and the coronary and peripheral blood vessels.

Disorders of body canals, such as coronary arteries for example, are
30 generally caused or provoked by the presence, on the inner walls of the
canal, of deposits which cause strictures or stenoses in said canal.

The treatment of such disorders generally calls for the use of an
35 20 inflatable device, such as a dilatation catheter for example, for restoring the
normal section of flow of the canal at the level of the stenosis. In a certain
number of cases, the result is further optimised through implantation of an
40 expandable device in order to provide support to the vessel wall.

Such expandable devices are well-known in the field of medicine for
25 implantation in blood vessels, biliary ducts, or indeed other similar organs
of the living body. They generally fall into two categories : those known as
45 self-expandable prostheses, and those which require a forced expansion
with the aid of a balloon for example ; both types are commonly known as
stents in the cardiovascular field. Such expandable devices are used to
50 30 maintain, open, or dilate tubular structures or to support tubular structures

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that are being anastomosed.

Although stents have in general shown to be very effective in restoring canal patency by virtue of a scaffolding role which counteracts the phenomenon of remodelling, the implantation of a stent provokes substantial vascular injury which in some cases leads to clinical symptoms and the necessity for medical reintervention. Subacute stent thrombosis remains a threat post-stent implantation in spite of improvements in drug regimens applied post-intervention. More importantly, the healing response of the arterial wall post implantation engenders the proliferation of smooth muscle cells and consequently the formation of neointimal hyperplasia which leads to inner stent-restenosis, a condition for which no satisfactory solution has yet been found.

Methods of inhibiting thrombus formation has been the subject of much research and publications in the literature. The object of the majority of this research has been into coated stents.

One of the methods described uses the concept of coating a stent with a polymer. Furthermore, the local delivery of therapeutic agent(s) using stents has centred around two concepts :

- i) directly coating the stent wires with a therapeutic agent or a therapeutic agent-polymer combination (Bailey *et al.*, Circulation, 1990, 82: III-541 ; Cavendar *et al.*, Circulation, 1990, 82 :III-541) ; and
- ii) incorporating a therapeutic agent into a stent that was constructed not of metal but of a biodegradable polymer (Murphy *et al.*, J. Invasive Cardiol., 1991, 3 : 144-148).

The major advantage of directly coating a device, such as a stent wire, with a therapeutic agent or a therapeutic agent-polymer combination is the low quantity of therapeutic agent necessary because the therapeutic agent is released close to the indwelling device.

Most efforts were focused upon directly coating the metal stent wires with a polymer. This polymer is usually placed directly on the stent

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(for example by the method disclosed in EP-A-0 797 963, which involves dipping the stent in a solution of a polymer in a solvent, followed then by the evaporation of the solvent) or is covalently bound to the metal. The polymer is bonded to or contains an anticoagulant compound. Most coated stents currently under development use heparin as the active ingredient. One of the more effective polymer coated stent is Biogold (van der Giessen *et al.*, Circulation, 1990, 82 :III-542). Biogold and other coated stents have not however completely prevented arterial thrombosis. This is probably due to the cracking of the polymer as the stent is expanded during deployment, saturation of the anticoagulant binding sites on the stent, and/or the inadequacy of heparin as an anticoagulant in the prevention of arterial thrombosis and/or too small quantities of therapeutic agent in comparison with the total surface of arteries wall covered by the stent. It is because of these inadequacies associated with polymer coatings directly applied to stent wires that there remains a great need to effectively prevent vascular response at the site of the stent.

US 5,383,928 (EMORY UNIVERSITY, United States of America) entitled "Stent sheath for local therapeutic agent delivery" discloses a stent sheath for local therapeutic agent delivery. More specifically, the patent discloses a sheath for encompassing at least a portion of a stent to locally deliver a drug to an arterial wall or lumen into which the stent has been inserted, comprising a polymer and a drug incorporated within the polymer, the polymer sheath encompassing at least a portion of the stent and having a thickness to allow controlled release of the drug.

The major disadvantage of the sheath according to this prior art document resides in the fact that in order to change the therapeutic agent or adapt the therapeutic agent release rate incorporated therein, it is necessary to change the entire sheath itself (thickness, nature of polymer(s) etc.). Consequently, the whole mechanical properties of the entire sheath would also be changed.

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The principal aim of the present invention therefore is to solve the technical problem consisting in providing a sleeve for encompassing an expandable device for introduction into a body canal of a patient, said sleeve being adaptable in every way to the needs of the patient's canal in question.

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More specifically, in order for said sleeve to be adaptable in every way to the needs of the patient's canal in question, the sleeve, preferably of polymeric nature, would have to meet the following requirements in being :

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10 (a) bio-compatible, it causing little or no response from the body canal in question;

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(b) non-biodegradable, it being required to remain without any change in its properties in contact with the body canal in question for a specified amount of time;

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15 (c) sufficiently elastic to be expandable, when wet with a body fluid for example, it being capable of being expanded to the dimensions of the body canal in question; but,

(d) sufficiently inelastic so as not to recoil from its expanded state;

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(e) of a sufficient mechanical strength so as it tears neither under expansion nor in the expanded state;

40

(f) of such a chemical nature that it is optionally able not only to be either coated or impregnated with any therapeutic agent(s) whatsoever in need of which the patient's body canal in question may be, said therapeutic agent(s) being capable of treating either a disorder of a body fluid flowing through the patient's body canal or a disorder of a body canal wall, or, more importantly, both, but furthermore of such a chemical nature that the rate of release of said therapeutic agent(s) be controlled at a rate pre-determinable according to the needs of the patient's body canal in question,

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30 (g) in the case where the therapeutic agent(s) are impregnated in

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the sleeve, the sleeve would have to be of a thickness pre-determinable according to the amount of therapeutic agent(s) it is desired to be released i.e. the thicker the sleeve, the more therapeutic agent(s) it may contain and release, and, finally,

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5 (h) able to optionally encompass an expandable device, a stent for example, it being possible for said expandable device to be either embedded within said sleeve, or disposed radially and internally with respect to said sleeve, according to the needs of the patient.

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The inventors of the present invention have carefully addressed the above-mentioned requirements and have been able to provide a solution to the present technical problem in the form of a sleeve which is comprised not of just a mixture of polymers, but a system of polymer layers.

25

More importantly, the sleeve in accordance with the present invention is comprised of a system of polymer layers which are actually able to adhere together without affecting the elasticity and mechanical properties of the sleeve resulting therefrom in any way whatsoever, and which thus provides a solution to the present technical problem in the form of a sleeve having highly advantageous properties over those of the prior art in a totally unexpected way.

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20 Thus, according to a first aspect, the present invention provides a sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that predetermined mechanical properties of said sleeve be provided.

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30 According to a second principal aspect, the present invention provides a sleeve for encompassing an expandable device for introduction

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10 into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.

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20
25 Advantageously, the mechanical properties of the resulting sleeve are thus governed by the at least one biocompatible, non-biodegradable elastic polymer layer, and the excellent biocompatibility of said sleeve are conferred thereto by the hydrogel inner and/or outer layers. Moreover, said sleeve, when wet with body fluid at 37°C is able to expand according to the needs of the patient's body canal, this being without any unsticking of the layers comprising said sleeve.

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20 Within the context of the present invention the term:

40 "non-biodegradable" is understood as meaning a polymer which does not fail the "environmental stress cracking", or "ESC". ESC has been attributed to biochemical and cellular interactions at the surface of the implanted material causing polymer chain cleavage. This may result in surface fissuring followed by deep cracking associated with considerable biodegradation of the polymer, resulting in loss of mechanical strength;

45 "biocompatible" is as defined by the US Pharmacopeia and refers to a polymer which successfully passes the USP Class V1 plastics testing; and

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30 "hydrogel" is understood as meaning a material which is hydrophilic

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in nature and which exhibits the characteristic macromolecular structure of a gel. A gel is best described as a continuous three-dimensional network that is held together by chemical or physical bonds. Sufficient interstitial space exists within the network, and water molecules can become trapped and immobilised, filling the available free volume. Gels can be divided into two major categories based on the types of bonds that comprise them. These include chemical gels and physical gels.

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Advantageously, the above-mentioned sleeve is characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a material selected from the group consisting of polyurethane, silicone, and latex. The material needs to have a good elasticity that is an elongation of at least 500% (PU tensile strength 7,500 psi elongation 500%, latex tensile strength 85 kg/cm² elongation 700%, silicone tensile strength 1310, elongation 1000%) and a good flexure resistance in vivo (no oxidation of the material even if the sleeve is stretched).

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The nature of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

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Also advantageously, the above-mentioned sleeve is characterised in that said hydrogel outer and inner layers independently comprise at least one hydrophilic polymer selected from the group consisting of polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

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Such hydrophilic polymers are particularly preferred within the context of the present invention because they possess a capacity to act as a vehicle for the therapeutic agent(s) useful for treating a body canal, and, more importantly, because they are able, once mixed with other polymers

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10 or cross-linked, to release the therapeutic agent(s) at a rate which is pre-determinable by easy selection of the thickness of said film or layer, and the ratio of therapeutic agent with the hydrogel.

15 The nature of the composition of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

20 An example of a particularly preferred hydrophilic polymer that may be used within the context of the present invention is poly

10 (N-vinylpyrrolidone), especially when the biocompatible, non-biodegradable elastic polymer layer is made of polyurethane. A particularly suitable material is produced under the trade name Hydromer and is made by the interaction of poly-vinylpyrrolidone (PVP) with one of several isocyanate prepolymers.

25 According to an advantageous embodiment of the present invention, the above-mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

30 According to a further advantageous embodiment of the present invention, the above mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

35 Within the context of the present invention, the term "therapeutic agent" is understood as meaning any compound which has a pharmacological effect.

40 Particularly advantageously, the above-mentioned sleeve is characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin
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55 compound, a platelet receptor antagonist, an anti-thrombin antibody, an

anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof ; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor antagonist, a transcriptional activator, a translational promoter, or a combination thereof ; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against growth factors, a bifunctional molecule consisting of a growth factor and a cytotoxin, and a bifunctional molecule consisting of an antibody and a cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a vasodilating agent, an agent which interferes with endogenous vasoactive mechanisms, or a combination thereof ; or a smooth muscle inhibitor, such as an agent which modulates intracellular calcium binding proteins, a receptor blocker for contractile agonists, an inhibitor of the sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor agonist, an antimitotic agent, an immunosuppressive agent, a protein kinase inhibitor, or a combination thereof ; or a combination thereof.

According to a third principal aspect, the present invention provides a system for introduction into a body canal, characterised in that it comprises an expandable device and a multi-layered sleeve in accordance with the present invention.

According to an advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is embedded within said biocompatible, non-biodegradable elastic polymer layer.

According to a further advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is disposed radially and internally with

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respect to said hydrogel inner layer.

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According to a particularly advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is a stent.

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5 The sleeve length may be of shorter or longer length than the expandable device optionally encompassed therein, or of course be of the same length.

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According to a fourth aspect, the present invention provides a system which is characterised in that it is intended to be introduced into a body canal comprising a canal wall and a lumen through which a body fluid flows and in that said sleeve comprises a hydrogel inner layer which can contain one or more therapeutic agents capable of treating a disorder of said body fluid, and a hydrogel outer layer which can contain one or more therapeutic agents capable of treating a disorder of said body canal wall.

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15 According to a fifth aspect a particularly advantageous method of manufacturing the sleeve of the invention comprises dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

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20 Various alternative methods of manufacture are described in more detail below in the Examples.

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The invention will be better understood and other objects, characteristics and advantages thereof will become more clearly apparent from the following explanatory description referring to the attached schematic drawings, which are given solely by way of non-limiting examples illustrating two preferred embodiments of the invention, and in which:

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30 Figure 1 is a longitudinal schematic view showing a system comprising a stent and a multi-layered sleeve according to a first preferred embodiment of the invention, in which said stent is disposed radially and

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internally with respect to said multi-layered sleeve, represented in a body canal;

Figure 1A is a view in cross section of Figure 1;

Figure 2 is a longitudinal schematic view, similar to Figure 1,

illustrating a second preferred embodiment of the sleeve according to the invention, in which the stent is embedded within the biocompatible, nonbiodegradable elastic polymer inner layer of said sleeve;

Figure 2A is a view in cross section of Figure 2.

In all Figures 1A, 1B, 2A, and 2B,

1 represents the at least one, optionally therapeutic agent(s)-containing, hydrogel outer layer of the multi-layered sleeve in accordance with the present invention,

2 represents the at least one biocompatible, non-biodegradable elastic polymer layer of the multi-layered sleeve in accordance with the present invention,

3 represents the expandable device for introduction into a body canal; and

4 represents at least one, optionally therapeutic agent(s)-containing, hydrogel inner layer of the multi-layered sleeve in accordance with the present invention.

The multi-layered sleeve is advantageously manufactured by a dipping process in which a mandrel is successively dipped in a solution in which there are different components, polymers and solvents. This successive dipping process builds up the different layers of the sleeve, as detailed above, and also ensures that, should an expandable device such as a stent be incorporated, such a device may, if required, be fully embedded in the finished sleeve. Layers which are required to be thicker than one dipping can provide are made by multiple dippings of the same component until the required thickness has been built up. Each dipping step consists in vertically immersing the mandrel in the different solutions

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using an automatic soaking machine. The thickness of membrane laid down at each dipping step is controlled by the following parameters:

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- the rate of insertion into the solution;
- the time resident in the solution;
- the rate of withdrawal from the solution;
- the concentration of the solution.

After each dipping step, the coated mandrel is subject to curing.

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During curing the following phenomena occur:

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- Cross-linking of the principal components.
- Solvent evaporation.

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It is important to ensure that the cross-linking is complete and that all of the solvent has been evaporated from the different layers. To ensure this, the temperature at which the curing takes place, and the duration of curing, may be controlled. At the completion of the processing, the sleeve

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is removed from the mandrel.

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The following examples give detail of the technique which is followed, it being understood that these are provided as an illustration of the technique used to prepare the sleeves according to the present invention and are in no way intended to limit the scope of the invention.

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EXAMPLE I:

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PREPARATION OF A SLEEVE WITH A HEPARIN-CONTAINING HYDROGEL INNER LAYER

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A 10% solution of polyurethane in N,N-dimethylacetamide is prepared. A 1.25 mm mandrel is dipped in the solution. The dipped mandrel is cured at 75°C in an oven for 20 minutes.

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The mandrel is dipped again in the solution. The mandrel is cured again at 75°C for 20 minutes. The mandrel is then dipped in the hydrophilic solution containing the heparin (3% of heparin benzalkonium chloride solution + PVP) and is then cured at 60°C for 30 minutes. The sheath is

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retrieved from the mandrel and reversed (i.e. turned inside out, or transposed). The membrane is inserted onto a transluminal prosthesis (stent).

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The transluminal prosthesis is placed onto a 3.5 PTCA catheter and is inflated at the 3.5 mm diameter.

The transluminal prostheses are then tested for anti-clotting properties in comparison with the transluminal prosthesis without the hydrogel inner layer.

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The inner surfaces were then extracted in human plasma at 37°C for 7, 10, 21 or 28 days and then tested for anti-clotting properties. The results obtained are shown in the Table.

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TABLE

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SAMPLE	CLOTING TIME (minutes)
Uncoated sample	12
coated sample without extraction of plasma	did not clot
coated sample with 7 days extraction in plasma	did not clot
coated sample with 10 days extraction in plasma	did not clot
coated sample with 21 days extraction in plasma	24
coated sample with 28 days extraction in plasma	20

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EXAMPLE 2:

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PREPARATION OF A SLEEVE WITH THE SAME HYDROGEL
INNER AND OUTER LAYERS

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A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

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polyvinylpyrrolidone 1 g
nitrocellulose 0.12 g
ethanol 9 ml
dimethylformamide 3.0 ml
ethyl acetate 0.4 ml

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A 1.25 mm diameter mandrel is dipped in the polyurethane solution.

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The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel is then dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

25

The sleeve is retrieved from the mandrel, reversed and put again onto the mandrel.

The mandrel is dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

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The sleeve is retrieved from the mandrel, cut and inserted onto a transluminal prosthesis (stent).

The transluminal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

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EXAMPLE 3: PREPARATION OF STENT INCLUDING SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS (According to Figure 2)

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A 10% solution of polyurethane in N,N-dimethylacetamide is prepared.

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25

A 1 mm diameter mandrel is dipped in the solution. The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

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The sleeve is retrieved from the mandrel, reversed and put back on the mandrel.

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The transluminal prothesis (stent) is put onto the mandrel and the sleeve and is crimped on it.

The mandrel is dipped again in the polyurethane solution. The mandrel is cured again at 75°C for 20 minutes.

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5 The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

The transluminal prothesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

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10 **EXAMPLE 4:**

PREPARATION OF A SLEEVE WITH HYDROGEL OUTER LAYER

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A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

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15 polyvinylpyrrolidone 1 g
nitrocellulose 0.12 g
ethanol 9 ml
dimethylformamide 3.0 ml
ethyl acetate 0.4 ml

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20 Two mandrels (A and B) of 1.25 mm in diameter are dipped in the polyurethane solution. The dipped mandrels are cured at 75°C in an oven for 20 minutes. The mandrels are dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel A is then dipped in the hydrophilic solution and cured for 30 minutes at 75°C.

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25 The sleeve is retrieved from the mandrels. A tensile test is done on the two wet sleeves at 37°C. The two curves are identical up to 1000% elongation.

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EXAMPLE 5:

PREPARATION OF A SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. A 2 mm, mandrel is dipped in a first hydrogel solution.

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes. The first and second hydrophilic solutions may or may not be the same solution.

EXAMPLE 6:

PREPARATION OF A STENT INCLUDING SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS (According to Figure 1)

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. Two hydrogel solutions are prepared as inner and outer layers.

The transluminal prosthesis (stent) is put onto a 2 mm mandrel.

The mandrel is dipped in a first hydrogel solution.

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes.

The stent sleeve is retrieved from the mandrel.

The transluminal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

The advantages of the sleeves according to the invention are that they provide a sheath to improve the surface of the stent and/or to locally deliver therapeutic agent(s) to an arterial wall or lumen. The covered transluminal prosthesis can be used advantageously in a coronary artery after an angioplasty procedure but also to treat a prostate cancer whereby

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a chemotherapeutic agent is released directly into the urethra via the transluminal prosthesis implanted as an endoluminal prosthesis. Since a sleeve according to the present invention is used for delivering the therapeutic agent(s) and not the transluminal prosthesis itself the quantities of therapeutic agent are bigger than can be achieved with a coated transluminal prosthesis.

Claims

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CLAIMS

1. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic, hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that pre-determined mechanical properties of said sleeve be provided.
2. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.
3. The sleeve according to claim 1 or 2, characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a synthetic material selected from the group consisting of polyurethane, silicone, and latex.
4. The sleeve according to any one of claims 1 to 3, characterised in that said inner and outer synthetic hydrogel layers independently comprise at least one hydrophilic polymer selected from the group consisting of

polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

5. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said biocompatible, non-biodegradable elastic polymer layer is between 25 and 60 μm , preferably between 30 and 40 μm .

6. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said hydrogel inner and outer layers is, in the dry state, between 7 and 20 μm .

7. The sleeve according to any one of claims 2 to 6, characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

8. The sleeve according to any one of claims 2 to 7, characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

9. The sleeve according to any one of claims 2 to 8, characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin compound, a platelet receptor antagonist, an anti-thrombin antibody, an anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor agonist, a transcriptional activator, a translational promoter, or a combination thereof; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against

5 growth factors, a bifunctional molecule consisting of a growth factor and a
cytotoxin, and a bifunctional molecule consisting of an antibody and a
10 cytotoxin, or a combination thereof; a cholesterol-lowering agent, a
vasodilating agent, an agent which interferes with endogenous vasoactive
5 mechanisms, or a combination thereof; or a smooth muscle inhibitor, such
15 as an agent which modulates intracellular calcium binding proteins, a
receptor blocker for contractile agonists, an inhibitor of the
sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a
20 phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor
10 agonist, an antimetabolic agent, an immunosuppressive agent, a protein kinase
inhibitor, or a combination thereof; or a combination thereof.

25 10. A system for introduction into a body canal, characterised in that it
comprises an expandable device and a multi-layered sleeve according to
any one of claims 1 to 9.

15 11. The system according to claim 10, characterised in that said
expandable device for introduction into a body canal is embedded within
30 said biocompatible, non-biodegradable elastic polymer layer.

12. The system according to claim 10, characterised in that said
35 expandable device for introduction into a body canal is disposed radially
20 and internally with respect to said inner hydrogel layer.

13. The system according to any one of claims 10 to 12, characterised
in that said expandable device for introduction into a body canal is a stent.

40 14. The system according to any one of claims 10 to 13, characterised
in that it is intended to be introduced into a body canal comprising a canal
25 wall and a lumen through which a body fluid flows and in that said sleeve
45 comprises a therapeutic agent(s)-containing hydrogel inner layer which
contains one or more therapeutic agents capable of treating a disorder of
said body fluid, and a therapeutic agent(s)-containing hydrogel outer layer
50 which contains one or more therapeutic agents capable of treating a
30 disorder of said body canal wall.

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15. A method of manufacturing a sleeve as claimed in any one of claims 1 to 9, said method comprising dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

16. A method as claimed in claim 15 in which said mandrel is first dipped in a polymer solution and thence cured to form said elastic polymer layer, thence dipped into a hydrogel solution and thence cured to form a hydrogel layer.

17. A method as claimed in claim 16 wherein, in order to form said polymer layer, multiple dippings into said polymer solution, with curing inbetween, are carried out until the desired thickness for the polymer layer is achieved.

18. A method as claimed in either one of claims 16 or 17 in which, following the formation of said hydrogel layer, the sleeve is removed from the mandrel, turned inside out, and put back again onto the mandrel, following which the coated mandrel is dipped in a hydrogel solution, which may or may not be the same as the first-mentioned hydrogel solution, and is then cured.

19. A method as claimed in claim 18 wherein, after the sleeve has been replaced on the mandrel after having been turned inside out, a stent is placed over the mandrel and sleeve prior to the dipping step.

20. A method as claimed in claim 15 in which said mandrel is first dipped in a hydrogel solution and thence cured to form a hydrogel layer, is then dipped into a polymer solution and is thence cured to form a polymer layer and is then dipped into a hydrogel solution which may or may not be the same as the first-mentioned hydrogel solution, followed by curing.

21. A method as claimed in claim 20 wherein prior to the first dipping in a hydrogel solution, a stent is placed over the mandrel so that said hydrogel layer is formed over the stent and mandrel.

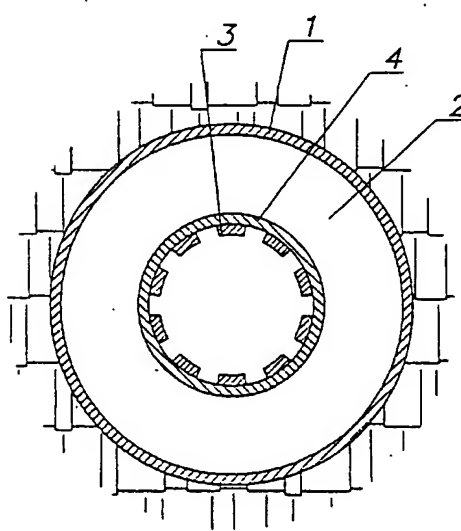
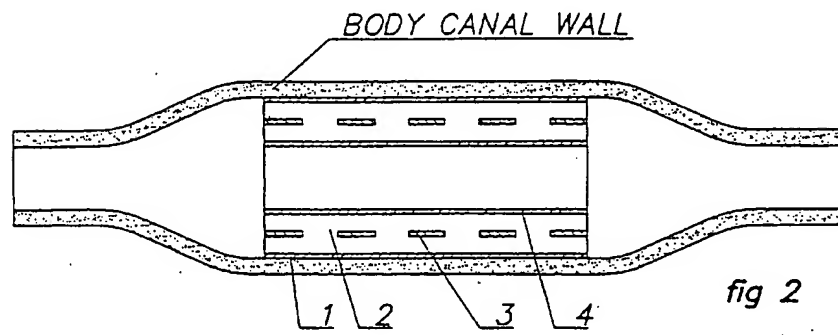
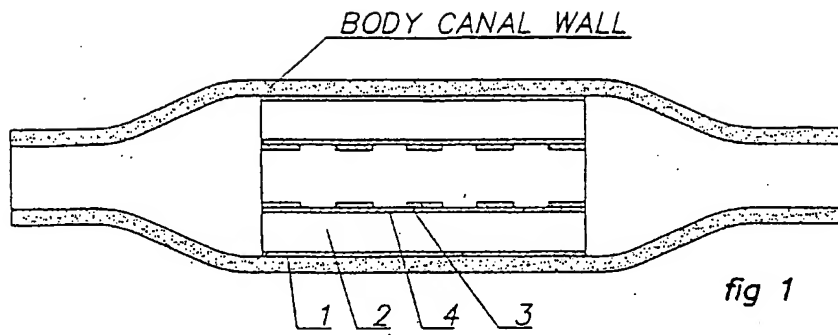


fig 1A

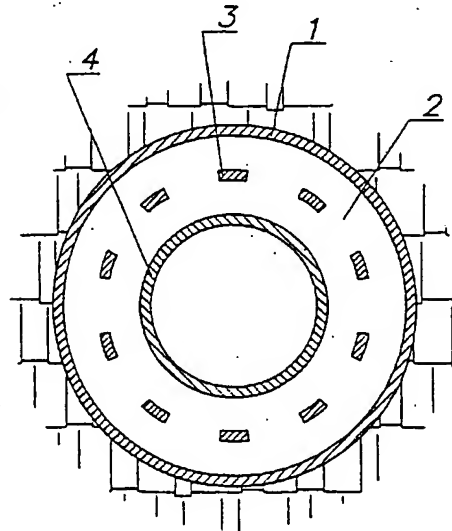


fig 2A

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 99/07156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L B05D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 29647 A (SCIMED LIFE SYSTEMS INC) 9 November 1995 (1995-11-09)	1-13
Y	figures 6,10,12 page 4, line 26 - line 30 page 5, line 9 - line 17 page 5, line 24 - line 27 page 6, line 18 - line 26 page 7, line 16 -page 8, line 20 page 13, line 23 -page 14, line 2	15-21
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/07156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International Application No

PCT/EP 99/07156

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